89 Rec'd PCT/PTO 04 AUG 1997
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

156-180

COMPLETION OF FILING NATIONAL PHASE OF PCT APPLICATION
UNDER RULE 35 USC 371 AND 37 CFR 1.494(c) OR 1.495(c)

#3

BOX PCT

COMPLETION
For PCT Cases Only

In re PATENT APPLICATION of

Inventor(s): Berscheid, et. al.

Appln. No.:	08	860,007
	Series Code	Serial No.

Atty. Dkt.	62-209-45694	45694
	M#	Client Ref

National Phase Filed:

Based on PCT	EP95	05068
		Country Code

(Our Deposit Account No. 06-0115)

(Our Order No.	27462	62-209-45694
	C#	M#

Title: BIOCIDAL ALCOHOLS, THEIR PRODUCTION AND THEIR USE

Date: August 4, 1997

FILING OF ITEM(S) LATE IN PCT/USA NATIONAL CASE

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

The following completes the filing of the subject application under Rule 494(c)/495(c). Please accept the following attached items:

1. Missing Requirements Notice (PCT/DO/EO/905) [X] copy attached [ ] not yet received

2. [X] **Signed Declaration** [X] Original [ ] Facsimile/Copy [ ] with spec/claims attached

3. [ ] **Translation** of the International Application into English including:

   a. [ ] Request; b. [ ] Abstract
   c. ____ pgs. Spec. and Claims; d. [ ] Translation verification
   e. ____ sheets Drawing which are [ ] informal [ ] formal of size [ ] A4 [ ] 11" [ ] 13" [ ] 14"

4. [ ] a copy of **International Search Report** (ISR) attached (_____ page(s))
   a. [ ] plus Annex of family members (_____ page(s))

5. **Information Disclosure Statement** including:

   a. [ ] Form PTO-1449 listing documents
   b. [ ] Copies of document(s) listed on Form PTO-1449
   c. [ ] A concise explanation of ISR references is given in the ISR

08/12/1997 WCLAYBRO 00000068 08860007
01 FC:156 130.00 OP

6. [X] **Assignment** and cover sheet. Please return the recorded assignment to the undersigned.

7. [ ] Copy of Power to international application agent

8. ____ (No.) Verified Statement(s) establishing "small entity" status under Rules 9 & 27.

Completion Under Rule 494(c)/495(c)

9. ☐ Formal Drawings: ____ sheet(s) ☐ informal; ☐ formal of size: ☐ A4 ☐ 11" ☐ 13" ☐ 14"

10. ☒ Please immediately start national examination procedures (35 USC 371(f))

11. ☐ Attached:

12. ☐ Preliminary Amendment:

13. ☒ Basic U.S. National fee per Rule 492(a)(1)-(4) was previously timely filed.

14. **Calculation of remaining fees due (if any)**: based on amended claim(s) per above item

☐ 12 (above) or item(s) (in CDC-112 filed previously) ☐ 12 ☐ 14 ☐ 17 ☐ 25

15. **CLAIMS FEES** ☒ previously paid ☐ paid herewith as follows:

				Large/Small Entity		Fee Code
16. Total Effective Claims		minus 20 =		x $22/$11	+	966/967
17. Independent Claims		minus 3 =		x $78/$39	+	964/965
18. If any proper multiple dependent claim (ignore improper) is present, add				$250/$125	+	968/969
19. Filing Declaration late, fee paid	previously	☒	now	$130/$65	+130	154/254
20.				SUBTOTAL =	$130	
21. **Original due date:**						
22. **Petition is hereby made** to extend the original due date to cover the date this response is filed for which the requisite fee is attached			(1 mo) (2mos) (3mos) (4mos)	$110/$55 $380/$190 $900/$450 $1400/$700	+	115/215 116/216 117/217 118/218
23.				TOTAL	$	
24. If "non-English" box 2 is X'd, add Rule 17(k) processing fee				$130	+	156
25. If "assignment" box 6 is X'd, add recording fee				$40	+	581
26.				TOTAL FEE ENCLOSED =	$130	

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.

Farkas & Manelli, PLLC
1233 20th Street, N.W. Suite 700
Washington, D.C. 20036-2396
Tel: (202) 778-1130

By: Atty: Jeffrey S. Melcher **Reg. No.** 35,950

Sig: 

Fax: (202) 887-0336
Tel: (202) 778-1247

NOTE: File in duplicate with PTO return receipts & attachments

08/860007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REQUEST FOR FILING NATIONAL PHASE OF
PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

To: The Commissioner of Patents and Trademarks
Washington, D.C. 20231

(Our Deposit Account No. 06-0115
(Our Order No. 27462 / 209-45694
C# / M#

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Atty. Dkt. 209-45694 / 45694
M# / Client Ref.

From: Farkas & Manelli, PLLC

Date: June 19, 1997

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application	2. International Filing Date	3. Earliest Priority Date Claimed
PCT/EP95 /05068	20 December 1995	21 December 1994
↑ country code	Day MONTH Year	Day MONTH Year
		(use item 2 if no earlier priority)

4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

(a) [ ] 20 months from above item 3 date (b) [X] 30 months from above item 3 date,

(c) Therefore, the due date (unextendable) is June 21, 1997

5. Title of Invention BIOCIDAL ALCOHOLS, THEIR PRODUCTION AND THEIR USE

6. Inventor(s) Ralf Berscheid, Heinz Eggensperger, Wolfgang Beilfuss, Sabine Behrends, Burghard Puchstein

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

7. [X] Please immediately start national examination procedures (35 U.S.C. 371(f)).

8. **[X] A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:

a. [ ] Request;
b. [X] Abstract;
c. 39 pgs. Spec. and Claims;
d. 0 sheet(s) Drawing which are [ ] informal [ ] formal of size [ ] A4 [ ] 13" [ ] 14"

9. **[X] A copy of the International Application has been transmitted by the International Bureau.**

10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))
a. [ ] is transmitted herewith including: (1) [ ] Request; (2) [ ] Abstract;
(3) ____ pgs. Spec. and Claims;
(4) ____ sheet(s) Drawing which are:
[ ] informal [ ] formal of size [ ] A4 [ ] 13" [ ] 14"
b. [X] is not required, as the application was filed in English.
c. [ ] is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.
d. [ ] Translation verification attached (not required now).

11. **[X] PLEASE AMEND** the specification before its first line by inserting as a separate paragraph:

--This application claims benefit of international application PCT/EP95/05068, filed December 20, 1995.--

12. [ ] Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file if in English but, if in foreign language, file only if not transmitted by the International Bureau) including:**

13. [ ] PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau.

14. [ ] Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered cancelled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. **[ ]** is submitted herewith [ ] Original [ ] Facsimile/Copy
b. [X] is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report** (ISR):
a. Was prepared by [X] European Patent Office [ ] Japanese Patent Office [ ] Other
b. [X] has been transmitted by the International Bureau to PTO.
c. [X] copy herewith (3 pg(s).) [X] plus Annex of family members (2 pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. [X] has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. [X] copy herewith in English
c.1 [X] IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 [X] Specification/claim pages # 7 [ ] Drawing Sheets #_____
c.3 [X] Which resulted in cancellation of pages # 36-39 Dwg Sheets #_____
d. [ ] Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered cancelled).**

18. **Information Disclosure Statement** including:
a. [X] Attached Form PTO-1449 listing documents
b. [X] Attached copies of documents listed on Form PTO-1449
c. [X] A concise explanation of relevance of ISR references is given in the ISR.

19. [ ] **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. [ ] Copy of Power to IA agent.

21. **[ ]** **Drawings:** ____ sheet(s) per set: [ ] 1 set informal; [ ] Formal of size [ ] A4 [ ] 13" [ ] 14"

22. [ ] ____ (No.) **Verified Statement(s)** establishing "small entity" status under Rules 9 & 27

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) Germany of:

Application No.	Filing Date	Application No.	Filing Date
(1) P 44 47 361.3	12/21/94	(4)_____	_____
(2) _____	_____	(5)_____	_____
(3) _____	_____	(6)_____	_____

a. [X] See Form PCT/IB/304 sent to US/DO with copy of priority documents
b. [ ] Copy of Form PCT/IB/304 attached.

24. Attached:

25. Preliminary Amendment:

Please amend the claims as follows:

Claim 3, line 1, delete "or 2";
Claim 4, line 1, replace "any of the preceding claim" with --claim 1,--;
Claim 5, line 1, replace "any one of claims 1 to 4" with --claim 1--;
Claim 6, line 2, replace "one of claims 1 to 5" with --claim 1--;
Claim 8, line 1, delete "or 7"; and
Claim 9, line 1, replace "any one of claims 6 to 8" with --claim 1--.

25.5 Per item 17.c3, **cancel original** pages #_____, claims # _____, Drawing Sheets #_____

26. Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:
based on amended claim(s) per above item(s) [ ] 12, [ ] 14, [X] 17, [X] 25 [ ] 25.5 (hilite)

			Large/Small Entity	Fee Code
TOTAL EFFECTIVE CLAIMS	12 - 20 = *0	x	$22/$11 = $0	(966/967)
INDEPENDENT CLAIMS	2 - 3 = *0	x	$80/$40 = $0	(964/965)

*If answer <0, enter "0"

If any proper (ignore improper) MULTIPLE DEPENDENT CLAIM is present, -------- add $260/$130 +0 (968/969)

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)):----------**BASIC FEE REQUIRED, NOW** →↓

A. If country code letters in item 1 are not "US", "BR", "BB", "TT" or "MX" ↓

See item 15a re: ↓

1. Search Report was not prepared by EPO or JPO ---------- add $1040/$520 +_____ (960/961)
2. Search Report was prepared by EPO or JPO ---------- add $910/$450 +910 (970/971)

27. **SUBTOTAL** = $910

28. If Assignment box 19 above is X'd, add Assignment Recording fee of --------$40.00 +_____ (581)

29. Attached is a check to cover the ----------**TOTAL FEES** $910

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached.

This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.

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By Atty: Jeffrey S. Melcher

Reg. No. 35,950

Sig: _____

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NOTE: File in duplicate with 2 postcard receipts & attachments.

Biocidal alcohols, their production and their use

The invention relates to biocidal alcohols, their production and their use. In particular, the invention relates to a group of antimicrobially, fungicidally and antimycobacterially effective alcohols, to a process for their production and to the use of these alcohols in disinfectants, antiseptics, antimycotics, deodorants and preservatives.

The antimicrobial action of aliphatic alcohols is sufficiently known. Their disinfecting action increases with increasing chain length and reaches an optimum, say, in the case of 1-octanol. Primary alcohols are generally more effective than the corresponding secondary alcohols, and these in turn surpass the action of the corresponding tertiary alcohols, i.e. the action decreases e.g. in the order n-butanol - sec. butanol - tert. butanol.

2-ethyl hexanol has proved particularly effective. Unfortunately, however, this alcohol has an intensive and unpleasant odour which cannot be masked in practice by adding various perfumes. Its use as an active ingredient in disinfectants or preservatives is therefore severely limited.

The alcohols usually used, ethanol, isopropanol and n-propanol usually have to be used in concentrations of more than 50 % by wt. for the disinfection of surfaces. To deactivate viruses which are important as regards hygiene - such as e.g. Hepatitis B - the alcohol contents of hand disinfectants have to be increased to above 80 % by wt.

Disinfectants with high alcohol contents have a series of disadvantages such as for example low flash points, inadequate material compatibility above all with plastics such as e.g. plexiglas, a rapid evaporation from the skin and surface areas

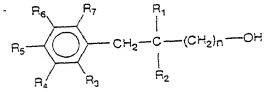
to be disinfected and thus no sufficient long term action, such as is e.g. indispensable for surgical hand disinfection, and an incompatibility with mucous membranes and wounds; concentrations of above 10 % by wt. already lead to an unpleasant burning.

From the series of alkyl aryl alcohols, benzyl alcohol, phenethyl alcohol and 3-phenyl-1-propanol are known to be antimicrobially effective. Benzyl alcohol is relatively easily oxidized to benzaldehyde which draws attention to itself in practice by its smell of bitter almonds. Phenethyl alcohol is the main constituent of rose oil and determines the character of the odour particularly when used for preserving cosmetics. Because of their weak action against fungi, both benzyl alcohol and phenethyl alcohol have to be combined with other active ingredients. 3-phenyl-1-propanol definitely presents itself as an antimicrobial active ingredient because of its pleasant and mild odour; however, its antimicrobial action, is unfortunately not sufficient for it to be used by itself as a disinfectant or preservative.

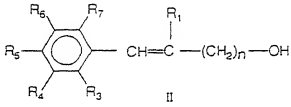
Also known is the antimicrobial action of the phenoxyalkanols, e.g. phenoxyethanol or 2-phenoxy-1-propanol. It is also used in practice for preserving cosmetics. The effectiveness - particularly against fungi - does however demand a relatively high use concentration. These alcohols have therefore to be combined with other active ingredients, e.g. with cationic compounds and/or aldehydes, particularly for the production of disinfectants.

It is therefore the object of the invention to find especially antimicrobially and fungicidally effective alcohols which, used alone or in combination with the aforementioned alcohols, produce disinfectants or preservatives which are characterized by a reduced total alcohol content, an excellent action against microorganisms - preferably against fungi - and an acceptable odour.

To achieve this object, the novel compounds (alcohols) of general formulae I and II are proposed according to claim 1:



I



II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

with the proviso, that in compounds of formula I

i) where R_1 and all groups R_3 to R_7 are hydrogen, then n = 2;

ii) where R_1 and R_2 are C_1-C_6 alkyl and all groups R_3 to R_7 are hydrogen, then n = 2;

iii) where R_1, R_2 and R_4 are methyl and all groups R_3 and R_5 to R_7 are hydrogen, then n = 2;

iv) where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is methyl or methoxy, then n = 2;

v) where R_1, R_3, R_6 and R_7 are hydrogen, R_2 is methyl and R_4 and/or R_5 are H or C_1-C_6 alkyl, then n = 2;

vi) where R_1 and R_4 to R_7 are hydrogen, R_2 is methyl and R_3 is methyl or methoxy, then n = 2;

vii) where R_1, R_3, R_5 and R_7 are hydrogen, R_2 is methyl, R_4 and R_6 are methyl or R_4 is hydrogen and R_6 is methyl, then n = 2;

and with the proviso, that in compounds of formula II

where R_1 is methyl or pentyl and all other groups R_3 to R_7 are hydrogen, then n = 2.

These alcohols can be produced in accordance with the process according to Claim 10 or 11.

Preferred embodiments are the subject-matter of the dependent claims.

It has surprisingly been shown that the action of the parent compound of the alcohols according to the invention, i.e. 3-phenyl-1-propanol or 4-phenyl-1-butanol or the corresponding propenols or butenols, in particular against fungi, is significantly increased when substituents are introduced into the 2-position in the case of the propanols, i.e. n = 1, or into the 3-position in the case of the butanols, i.e. n = 2, and optionally additionally into the aromatic core.

In preferred embodiments

R_2 is selected from C_1-C_5 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_5 alkenyl and C_3-C_5 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is hydrogen, fluorine, chlorine or bromine,

and preferably

R_2 is methyl ethyl, ethenyl, propyl, propenyl, propargyl, butyl and amyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, is hydrogen, methyl-X-, ethyl-X-, ethenyl-X-, propyl-X-, propenyl-X-, propargyl-X, isopropyl-X, isopropenyl-X-, t-butyl-X-, methoxymethyl-X-, methoxyethyl-X-, ethoxymethyl-X-, ethoxyethyl-X-, methoxypropyl-X- or ethoxypropyl-X-, where X is -O- or -S-.

It is preferred that n = 1.

Any combinations of groups according to the above definitions are also possible.

These alcohols according to the invention are suitable as antimicrobial and fungicidal active ingredients for disinfectants, antiseptics, antimycotics, deodorants and preservatives.

The invention covers also a composition which contains at least one of said compounds of formula I or II and a compound selected from alcohols, surfactants and solvents. It is preferred that the composition contains a compound of formula I or II in a quantity of 0.01 to 10 % by wt., in particular 0.05 to 8 % by wt. and preferably 0.1 to 5 % by wt. More preferred a composition according to the invention contains

a) 0.01 to 10 % by wt. of a compound of formula I or II, and

b) 0.1 to 90 % by wt. of a compound selected from C_1-C_6 alkyl alcohols, unsubstituded or substituted with a C_6-C_{12} aryl, aralkyl or aryloxy group, anionic, cationic, amphoteric or nonionic surfactants, dimethylformamide, betaines and glycerine.

Preferred compounds summarized in b) are, for example, ethyleneglycol ethers such as "Rewopal MPG 40" (which is tetraethyleneglycol monophenyl ether), ethoxylated higher alkyl alcohols such as "Brij 58" (which is polyoxyethylene-20-cetylalcohol), ethanol, 1-propanol, 2-propanol sulfosuccinate, betaine, phenoxyethanol and phenethylalcohol.

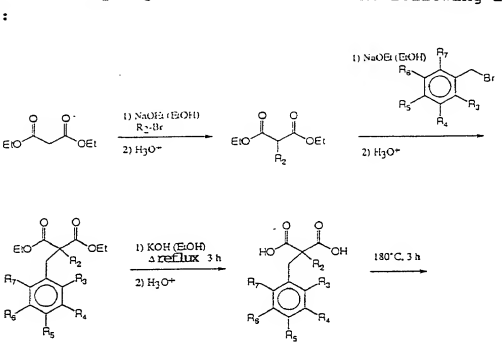
Said alkyl alcohols or mixtures thereof may be present in an amount of 20 to 85 % by wt., specifically 25 to 80 % by wt. Said surfactants or mixtures thereof may be present in an amount of 1 to 30 % by wt., specifically 5 to 25 % by wt. The other mentioned compounds may each be present in an amount of 0.1 to 20 % by wt., specifically 0.5 to 20 % by wt, e.g. 1.0, 2.0 or 3.0 and up to 10 or 12 % by wt.

The invention also covers the production of said compounds of formula I or II. Described in DE 35 31 585 is the production of such alcohols using Grignard reactions. However, the disadvantages of Grignard reactions are adequately known.

The process according to the invention offers several advantages over the Grignard processes. It is particularly advantageous that according to the invention all alcohols of general

formula I can be produced according to the same process. This is a malonic ester synthesis with subsequent decarboxylation and reduction. In the case of n = 2, the alcohols of general formula I can be obtained via the compounds of formula II using alkylation instead of hydrogenation.

This uniform and simple process consists of the following reaction steps:



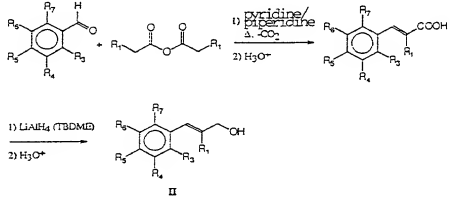
1. Alkylation of dialkyl malonate, preferably diethyl malonate with an alkyl halide, preferably a bromide, to give the monosubstituted malonic ester, as a result of which the group R_2 is introduced.

2. Second alkylation with an aryl-substituted benzyl halide, preferably a chloride or bromide, as a result of which the groups R_3 to R_7 are introduced, provided they are not hydrogen.

3. Saponification and subsequent decarboxylation to give the 3-aryl-substituted propionic acid and treatment by distillation of same.

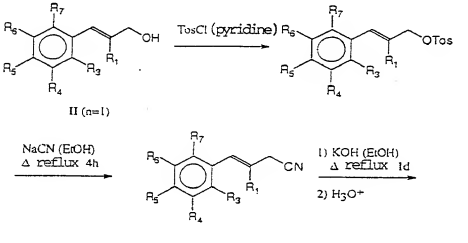
4. Reduction to the desired alcohol of formula I, e.g. with lithium aluminium hydride in diethyl ether or tert.-butyl methylether.

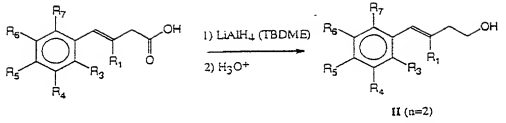
The alcohols of formula II with n = 1 can for example be obtained via a Perkin condensation reaction of a corresponding aromatic aldehyde with anhydrides with simultaneous decarboxylation and subsequent reduction of the acid in question with lithium aluminium hydride.



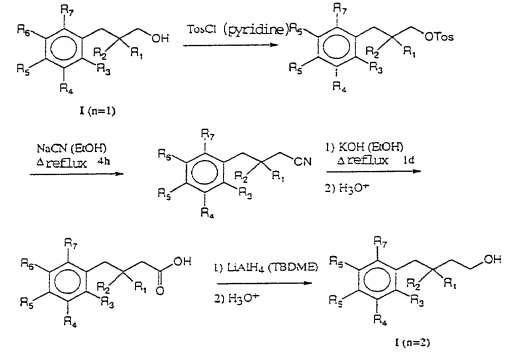
II

The alcohols of formula II with n = 2 are obtained for example from the respective alcohols with n = 1 via a chain elongation. The tosylate of alcohol II (n = 1) is substituted nucleophilically by NaCN and saponified. The resulting acid can be reduced with lithium aluminium hydride to the desired alcohol II (n=2).

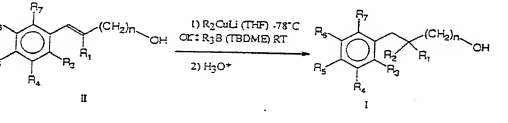




The alcohols I with n = 2 can be obtained in analogous manner.



By reducing alcohols of formula II with a reducing agent such as lithium aluminium hydride or alkylation agents such as lithium dialkyl cuprate or trialkyl boron, the alcohols of formula I can be obtained.



General synthesis instructions for alcohols of formula I using malonic acid diethyl ester

1. General instructions for the first alkylation of malonic acid diethyl esters:

200 mmol malonic acid diethyl ester and 200 mmol R_2-alkyl bromide (or chloride) are introduced first into a 250 ml triple-necked flask with internal thermometer, reflux condenser and dropping funnel and the whole is cooled to 10 to 15°C. 68.05 g (200 mmol) 20 % NaOEt in EtOH are slowly added dropwise (over 30 minutes) via a dropping funnel so that the temperature does not exceed 20°C. The mixture is then stirred for a further 30 minutes at 20°C and finally heated to 50 to 60°C for 1 hour. After cooling, the mixture is neutralized with glacial acetic acid (optionally cooling; pH monitored until the buffer pH value is reached). The resulting NaBr is separated off with a frit and then washed with a little cold EtOH. The main quantity of alcohol in the filtrate is distilled off at normal pressure. The filtrate is mixed with 50 ml H_2O and 1 ml conc. HCl, and the organic and the aqueous phases are separated from one another. The organic phase is kept for further use (see below) and the aqueous phase is extracted with 2 x 50 ml ether (if phase separation does not take place, the filtered-off NaBr is used to increase the density, as a result of which a phase separation is initiated). The combined organic phases are dried over sodium sulphate and the solvent is removed in a vacuum. The thus-formed crude product (R_2-substituted malonic ester) can be further used directly for the subsequent saponification.

2. General instructions for the second alkylation of alkyl malonic acid diethyl esters:

200 mmol R_2-substituted malonic acid diethyl ester and 200 mmol R_3-R_7-substituted benzyl bromide (or chloride) are introduced first into a 250 ml triple-necked flask with internal thermometer, reflux condenser and dropping funnel and the whole is

cooled to 10 to 15°C. 68.05 g (200 mmol) of 20 % NaOEt in EtOH are slowly added dropwise (over 30 minutes) via a dropping funnel so that the temperature does not exceed 20°C. The mixture is then stirred for a further 30 minutes at 20°C and finally heated to 50 to 60°C for 1 hour. After cooling, the mixture is neutralized with glacial acetic acid (optionally cooling; pH monitored until the buffer pH value is reached). The resulting NaBr is separated off with a frit and then washed with a little cold EtOH. The main quantity of alcohol in the filtrate is distilled off at normal pressure. The filtrate is mixed with 50 ml H_2O and 1 ml conc. HCl, and the organic and the aqueous phases are separated from one another. The organic phase is kept for further use (see below) and the aqueous phase is extracted with 2 x 50 ml ether (if phase separation does not take place, the filtered-off NaBr is used to increase the density, as a result of which a phase separation is initiated). The combined organic phases are dried over sodium sulphate and the solvent is removed in a vacuum. The thus-formed crude product (disubstituted malonic ester) can be further used directly for the subsequent saponification.

3. General instructions for the saponification of disubstituted malonic esters:

100 mmol of the disubstituted malonic ester are refluxed with a solution of 45 g conc. KOH (45%) and 50 ml EtOH for 3 hours. The main quantity of ethanol is distilled off under weak vacuum, the remaining residue is dissolved in H_2O until the water is clear and conc. HCl is added dropwise, accompanied by cooling with ice, until the pH value is 1. The aqueous phase is extracted with 100 ml and then 2 x 50 ml ether. The combined organic phases are dried over sodium sulphate, the solvent is removed in a vacuum and the remaining oil is dried over night in a desiccator. The crude product (disubstituted malonic acid) can be further used for the subsequent decarboxylation without further purification; small residual quantities of ethanol or water do not cause disturbance.

4. General instructions for the decarboxylation of disubstituted malonic acids:

The disubstituted malonic acid is heated for 3 hours at 180°C (CO_2 cleavage). Residual quantities of ethanol and H_2O and fruit esters are then distilled off at normal pressure (bath temperature 230 to 250°C). After applying a vacuum (20 to 25 mbar) the 2,3-disubstituted propionic acid is subjected to fractional distillation. To remove moisture that has distilled over and not very volatile components, the distillates can be dried in a desiccator.

5. General instructions for reducing disubstituted propionic acids with lithium aluminium hydride:

3.13 g (82.5 mmol) $LiAlH_4$ are introduced first into 100 ml of abs. ether. 100 mmol 2,3-disubstituted propionic acid in 50 ml ether are then slowly added dropwise (possibly with cooling), so that the ether boils easily. After the addition is finished, the mixture is stirred for a further 1 h at room temperature and then refluxed for 4 h. The cooled reaction mixture is carefully introduced with stirring into 200 ml iced water and stirred until the evolution of hydrogen is no longer to be observed. The whole is then mixed with 50 ml 10 % H_2SO_4, as a result of which the aluminium hydroxide precipitate dissolves. The phases are separated and the aqueous phase is extracted with 3 x 100 ml ether. The combined organic phases are washed with 3 x 50 ml of semi-concentrated NaOH and 2 x 50 ml saturated NaCl solution, dried over sodium sulphate and the solvent is removed in vacuum. The 2,3-disubstituted propanol is purified by distillation.

Synthesis examples

Selected as synthesis examples were

(±)-2-benzyl butanol (R_1=H; R_2=Et; R_3=R_4=R_5=R_6=R_7=H),

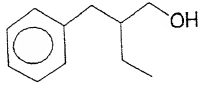
(±)-2-(3-methylbenzyl) butanol (R_1=H, R_2=Et; R_3=H; R_4=Et; R_5=R_6=R_7=H)

and

(±)-2-(3-chlorobenzyl) butanol (R_1=H, R_2=Et; R_3=H; R_4=Cl; R_5=R_6=R_7=H).

(±)-2-benzyl butanol:

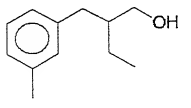
20 % total yield; colourless liquid with weak, pleasant odour; d = 0.975; n_D20 = 1.5178; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), approx. 1.65 (m; 1H, C*H*), 2.30 (s; 1H, O*H*), 2.60 (d; 2H, ArCH_2), 3.45 (d; 2H, CH_2OH), 7.0-7.4 ("s"; 5H, Ar*H*).

(±)-2-(3-methylbenzyl) butanol:

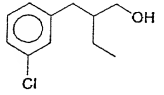
16 % total yield; colourless liquid with slight lily of the valley-type odour; d = 0.963; n_D20 = 1.5152; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), approx. 1.6 (m; 1H, C*H*), 2.25 (s; 3H, ArCH_3), 2.40 (s; 1H, O*H*), 2.55 (d; 2H, ArCH_2), 3.45 (d; 2H, CH_2OH), 6.7-7.2 (m; 4H, Ar*H*).

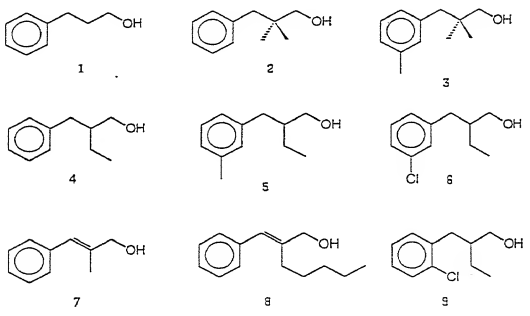
(±)-2-(3-chlorobenzyl) butanol:

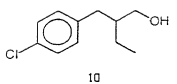
16 % total yield; slightly yellow liquid with discreet, pleasant odour; d = 1.099; n_D20 = 1.5322; IR corresponds to the structure.



^{1}H-NMR: 0.90 (t; 3H, CH_2CH_3), 1.30 (dq; 2H, CH_2CH_3), 1.55 (m; 1H, CH), 2.55 (d; 2H, $ArCH_2$), 3.30 (s; 1H, OH), 3.45 (d; 2H, CH_2OH), 6.9-7.2 ("s"; 4H, ArH).

Formulae of the alcohols treated below:





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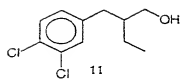

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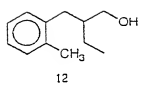

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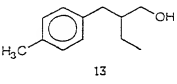

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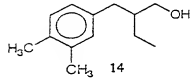

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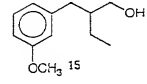

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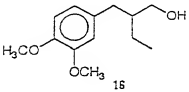

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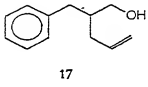

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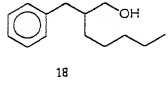

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Applications

1. **MIC (minimum inhibiting concentration) values**

a) **MIC values, water-soluble**

Standard formulation:

-	Rewopal MPG 40	25.0 g
-	aromatic alcohol	10 mmol
-	dem.* water	to 100 g
-	lactic acid for adjusting the pH value to 7.0	q.s.

(*dem. = demineralized)

Test germs:	Staphylococcus aureus	ATCC 6538
	Proteus vulgaris	NCTC 4635
	Candida albicans	ATCC 10231
	Penicillium funiculosum	ATCC 36839
	Aspergillus niger	ATCC 6275

Test method:

In sterile test tubes, 5 ml each of the dilutions of the disinfectant in WSH (water of standardized hardness) are mixed with 5 ml double-concentrated casein peptone soybean flour peptone solution (CSL) or CSL and deactivating substances.

To determine the bacteriostatic action on Staphylococcus aureus and Proteus mirabilis the tubes are inoculated by adding 0.1 ml of a CSL culture diluted 1:10 with CSL and incubated for 24 h at 37°C.

To test the fungistatic action, 0.1 ml of an undiluted CSL culture of Candida albicans which has been incubated at 37°C for 72 h is used in each case. Evaluation takes place after 72 h at 37°C.

The highest dilution of the preparation in CSL or CSL and deactivating substances that still suppresses growth of the test germs after 12 h incubation serves as the measure of the multiplication-inhibiting action (inhibition titre).

In the case of the disinhibition tests, the culture media are to be adjusted to a pH value of 7.0 ± 0.2 according to the state of the disinfectant.

Data in µmol/100 ml test solution

	S. aureus	P. vulgaris	C. albicans	P. funi.	A. niger
Blank value	2,500	1,250	1,250	625	1,250
1	1,250	625	625	313	625
2	313	313	313	313	313
3	2,500	2,500	625	156	156
4	313	2,500	313	156	156
5	156	2,500	313	156	156
6	156	2,500	156	78	156
7	625	2,500	313	156	313
8	39	1,250	313	313	156

Standard formulation:

- aromatic alcohol 5.0 %
- Brij 58 5.0 %
- 1,3-butanediol to 100

Test germs: see above
Test method: see above

Data in µmol/100 ml test solution

Compd. No.	S. aureus	P. vulgaris	C. albicans	P. funi.	A. niger
Blank value	2,500	1,250	1,250	625	1,250
1	1,250	625	625	313	625
3	625	625	625	313	625

Compared with the parent compound 3-phenyl propanol (alcohol 1), the alcohols 2-8 according to the invention clearly display

microbistatic activities, particularly alcohols 2, 6 and 8, in almost ten times lower a use concentration.

b) MIC values, water-insoluble

Solutions of the aromatic alcohols in acetone (w/w)

Test germs:	Staphylococcus aureus	ATCC 6538
	Escherichia coli	ATCC 11229
	Candida albicans	ATCC 10231
	Aspergillus niger	ATCC 6275

Test method: as under 1.; the dilution solutions were prepared in acetone.

The size of the covered areas of the plates is given in %; 100% means no inhibiting action.

Alcohol	Concentration [% by wt.]	S. aureus	E. coli	C. albicans	A. niger
Blank value	0.00	100%	100%	100%	100%
9	1.00	90%	100%	10%	20%
	0.50	100%	100%	100%	90%
	0.25	100%	100%	100%	100%
10	1.00	10%	100%	10%	10%
	0.50	100%	100%	90%	70%
	0.25	100%	100%	100%	90%
	0.125	100%	100%	100%	100%
11	1.00	5%	80%	10%	10%
	0.50	90%	100%	10%	70%
	0.25	100%	100%	100%	100%
12	1.00	90%	100%	80%	80%
	0.50	100%	100%	100%	100%
13	1.00	90%	95%	90%	20%
	0.50	100%	100%	100%	90%
	0.25	100%	100%	100%	100%
14	1.00	30%	100%	80%	80%
	0.50	90%	100%	100%	10%
	0.25	100%	100%	100%	90%
	0.125	100%	100%	100%	100%
15	1.00	100%	100%	100%	90%
	0.50	100%	100%	100%	100%
17	1.00	100%	80%	100%	80%
	0.50	100%	100%	100%	100%
18	1.00	0%	100%	70%	0%
	0.50	20%	100%	80%	40%
	0.25	100%	100%	100%	100%

Alcohols 11 and 13 display a very good broad activity spectrum. In contrast, alcohols 10, 14 and 18 display a very good selective action, in particular against fungi and yeasts.

2. Antimicrobial effectiveness in the plate diffusion test

Standard formulation:

- aromatic alcohol 1 part
- dimethylformamide 6 parts

Test germs:		
	Staphylococcus aureus	ATCC 6538
	Pseudomonas aeruginosa	ATCC 15442
	Proteus mirabilis	ATCC 14153
	Escherichia coli	ATCC 11229
	Candida albicans	ATCC 10231

Test method: Agar diffusion test

The diameters of the inhibition zones are given in mm.

Alcohol	S. aureus	P. aeruginosa	P. vulgaris	E. coli	C. albicans
Blank value	0	0	0	0	0
9	16	0	0	18	15
10	16	0	0	11	15
11	18	0	0	0	13
12	20	18	13	17	22
13	16	13	14	13	15
14	18	18	0	15	22
15	18	15	18	18	23
16	18	18	17	17	22
17	16	12	13	13	17
18	11	0	0	0	11

Alcohols 12, 15 and 16 show a very strong inhibition of the tested germs, alcohols 13, 14 and 17 showing a strong inhibition.

3. Use in an alcoholic surface disinfectant

Standard formulation:

- ethanol (MEK denatured) 25.0 %
- 1-propanol 35.0 %
- perfume 0.02 %
- benzotriazole 0.001 %
- Marlipal 013/70 0.1%
  (isotridecanpolyethyleneglycol-(7)-ether = C_{13} oxo alcohol + 7 mol ethylene oxide)
- active ingredient additive x%
- dem. water to 100

Test germ: Ps. aeruginosa
Test method:

Quantitative surface test according to DGHM (Deutsche Gesellschaft für Hygiene and Microbiology = German Association for Hygiene and Microbiology). In order to exclude the effectiveness of the readily volatile alcohol components (ethanol, 1-propanol), the preparations were deposited onto the surfaces and the germs were deposited after approx. 20 minutes.

Test surfaces: PVC and OP tiles
Data as reduction factors (log stages)

Additive	PVC			Tiles		
	30'	60'	240'	30'	60'	240'
without additive	0	0	0	0	0	0
0.05 % phenoxyethanol	0	0	0	0	0	0
0.05% phenoxyethanol 0.01% imidazole	0	0	0	0	0	0
0.125% Vantocil IB (polyhexamethylene biguanid hydrochlorid) 0.025% sorbic acid	0	0	0	0	0	0
0.027% Hostapur SAS (sec.alkanesulphonate-Na-salts based on n-paraffins) 0.006% Na-laurylether sulphate 0.017% malic acid	0	0	0	0	0	0
0.05% 3-phenyl propanol (1)	0	0	0	0	0	0
0.05% 2,2-dimethyl-3-phenyl-1-propanol (2)	>6.0	>5.4	>6.5	4.1	4.9	>5.8

Only the preparation with an aromatic alcohol of the formula I according to the invention, 2,2-dimethyl-3-phenyl-1-propanol (2) has an effectiveness against Pseudomonas aeruginosa on PVC and tiles that increases with increasing action time.

The other preparations are disinfectant solutions.

4. Use in a foot spray with deodorizing action and simultaneous prevention of athlete's foot

Formula:

- 2-propanol 40.0%
- aromatic alcohol 0.2 %
- allantoin 0.5 %
- dem. water to 100

Test germs: special skin fungi such as Trichophyton rubrum, Trichophyton mentagrophytes (ATCC 9533), Microsporon gypseum

Test method: Determination of the minimum inhibition concentration (method see under 1.) Data in %

Alcohol	T. rubrum	T. mentagrophytes	M. gypseum
Blank value	12.5%	6.25%	6.25%
1	6.25%	6.25%	6.25%
6	1.56%	1.56%	3.13%
8	1.56%	1.56%	1.56%

Test germs: special skin fungi such as Trichophyton rubrum, Trichophyton mentagrophytes, Microsporon gypseum

Test method: Agar diffusion test
Data as millimetres inhibition zone

Alcohol	Use concentration	T. rubrum	T. mentagrophytes	M. gypseum
Blank value	100%	0 mm	0 mm	0 mm
1	100%	0 mm	0 mm	0 mm
6	100%	12 mm	15 mm	13 mm
8	100%	23 mm	22 mm	19 mm
	50%	14 mm	14 mm	10 mm

With typical fungi which are relevant as regards skin, the formulations with alcohols 6 and 8 according to the invention show a very good action both in the MIC test and in the agar diffusion test. The aforementioned formulations are thus suitable for use in deodorants and products for the prevention of athlete's foot.

The parent compound 3-phenyl propanol shows almost similar values as the blank value, i.e. is ineffective.

5. Preservative

Standard formulation:

- sulfosuccinate 12.0%
- betaine 3.0%
- aromatic alcohol 0.5%
- re-fatting agent
- skin care additives
- thickener
- dem. water to 100

Test germs: Germ mixture of Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, Klebsiella pneumoniae, Enterobacter gergoviae, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas putida, Aspergillus niger,

Penicillium funiculosum, Candida albicans;
Total germ count 10^8-10^9/ml.

Test method: weekly loading of the sample with germ suspension; smear onto CS and Sabouraud agar. See also K.-H. Diehl, P. Oltmanns, J. Ramsbotham, Seife, Öle, Fette, Wachse 118 (1992) 546.

Data expressed semi-qualitatively:

-	no growth	< 10^2 CFU/g	(CFU = colony-forming units)
+	slight growth	approx. 10^3 CFU/g	
++	moderate growth	approx. 10^4-10^5 CFU/g	
+++	heavy growth	> 10^5 CFU/g	

Alcohol	1st week	2nd week	3rd week	4th week	5th week
Blank value	+++	+++	+++	+++	+++
Phenoxyethanol	-	-	-	-	-
1	-	-	-	-	-
2	-	-	-	-	-

Preservation with 0.5 % 2,2-dimethyl-3-phenyl propanol (2) is just as effective as that with the known preservative phenoxyethanol, but displays a more sure (more quickly acting) preservation in the first two weeks compared with the parent compound 3-phenyl propanol.

The alcohols according to the invention are thus suitable as a preserving additive in shampoos and shower gels.

6. Mucous membrane antiseptic

Standard formulation:

-	Cocamidopropyl betaine (30%)	3.0 %
-	glycerin DAB 10 (85%)	0.5%
-	phenoxyethanol	1.0%
-	arom. alcohol	0.5%
-	dem. water	to 100
-	NaOH to adjust the pH value to 5.5	q.s.

Test germs: Pseudomonas aeruginosa ATCC 15442
Staphylococcus aureus ATCC 6538

Test method: Quantitative suspension test according to DGHM

Data as reduction factors (log stages); C = control

pH 5.5	Alcohols:	none (blank value)			1			2			3			8		
Test organisms	Contact time [min]	C	100	50	C	100	50	C	100	50	C	100	50	C	100	50
Staphylococcus aureus	30''	6.7	0	0	6.6	2.7	1.1	6.6	1.3	0	6.6	2.0	1.0	6.7	2.7	0
	1'	6.7	0	0	6.6	3.2	1.2	6.6	4.6	1.8	6.6	3.4	1.4	6.7	3.9	0
	2'	6.7	1.3	0	6.6	4.1	1.6	6.6	5.6	2.8	6.7	3.8	2.0	6.7	5.1	0
	5'	6.6	2.1	0	6.7	5.2	1.9	6.8	>5.8	4.4	6.7	4.9	3.3	6.8	>5.8	2.6
Pseudomonas aeruginosa	30''	6.5	3.3	0	6.5	>5.5	0	6.6	3.7	0	6.4	2.3	0	6.5	4.0	0
	1'	6.5	4.1	0	6.5	>5.5	0	6.6	5.2	0	6.5	2.7	0	6.5	4.4	0
	2'	6.6	4.5	0	6.5	>5.5	1.1	6.4	>5.4	0	6.4	2.9	0	6.6	5.0	0
	5'	6.6	5.6	0	6.6	>5.6	1.3	6.6	3.6	0	6.6	3.7	0	6.6	5.6	0
Candida albicans	30''	5.9	0	0	6.1	1.0	0.7	5.9	1.6	0.6	5.9	2.9	0.7	5.9	1.9	0
	1'	6.1	0	0	6.4	1.8	1.1	5.5	2.3	0.1	5.5	4.0	0.3	6.1	2.9	0
	2'	6.0	0	0	5.8	2.7	0.4	5.4	2.4	0.1	5.4	>4.4	0.4	6.0	3.4	1.1
	5'	6.0	0	0	5.9	4.9	0.4	5.3	4.9	0.2	5.3	>4.3	0.9	6.0	5.0	2.0

The alcohols according to the invention significantly increase the effectiveness against the aforementioned germs, in particular against yeasts.

7. Skin antiseptic

a) standard formulation:

- 1-propanol	30.0%
- 2-propanol	45.0%
- aromatic alcohol	1.0%
- dem. water	to 100

Test germ: Microsporon luteus ATCC 15442

Test method: Apply 0.2 ml preparation to 10cm^2 skin, allow to dry, cover with TEGADERM® film and leave to work for 1 h, contaminate with 0.1 ml germ suspension, remove after 15 minutes with ring method

Reference: Control against Neo-Kodan®

Number of subjects: 10 subjects

Data as average value of the reduction factors (RF in log stages) of all 10 subjects

aromatic alcohol	Average value of RF
1.0% phenyl propanol (1)	0
1.0% α-amyl cinnamyl alcohol (8)	1.9
Reference: Neo-Kadan®	1.9

The formulation with 1.0% α-amyl cinnamyl alcohol (8) also shows the same values in the suspension test according to DGHM as the skin antiseptic Neo-Kadan® used for reference of 50%, 30 seconds, and likewise shows an equal action against the resident skin flora (100%, 15 seconds).

Moreover, the aforementioned results show that an action against the transient flora is only guaranteed when the α-amyl cinnamyl alcohol (8) substituted according to formula II is used and not the parent compound 3-phenyl propanol (1).

b) Standard formulation:

-	1-propanol	15.0%
-	2-propanol	30.0%
-	aromatic alcohol	1.0%
-	dem. water	to 100

Test germs:	Staphylococcus aureus	ATCC 6538
	Pseudomonas aeruginosa	ATCC 15442
	Candida albicans	ATCC 10231

Test method: Quantitative suspension test according to DGHM

Data as reduction factors (log stages)

		Blank value (0% 8)				1.0% 8		
Test organisms	Contact time [min]	C	75	50	25	75	50	25
Staphylococcus aureus	30''	6.6	>5.6	>5.6	0	>5.6	>5.6	2.8
	1'	6.6	>5.6	>5.6	0	>5.6	>5.6	3.6
	2'	6.9	>5.9	>5.9	0	>5.6	>5.6	4.7
	5'	6.6	>5.8	>5.8	0	>5.6	>5.6	>5.8
Pseudomonas aeruginosa	30''	6.6	>5.6	>5.6	0	>5.6	>5.6	0
	1'	6.6	>5.9	>5.9	0	>5.9	>5.8	0
	2'	6.7	>5.7	>5.7	0	>5.7	>5.7	0
	5'	6.7	>5.7	>5.7	0	>5.7	>5.7	0
Candida albicans	30''	6.6	>4.6	0.9	0.2	>4.6	2.7	0.6
	1'	5.6	>4.6	1.5	0	>4.6	3.5	0.6
	2'	5.9	>4.9	2.4	0.4	>4.9	>4.9	1.1
	5'	6.1	>5.1	3.5	0	>5.1	>5.1	1.7

In the aforementioned propanol-reduced formulation, the additional action of the α-amyl cinnamyl alcohol is seen in particular in the case of Candida albicans.

8. Use in an alcoholic disinfectant for surgical hand disinfection

Formulation:

- ethanol 80.0%
- phenethyl alcohol 2.0%
- 2,2-dimethyl-3-(3-methylphenyl) propanol (3) 0.4%
- re-fatting agent
- humectant
- dem. water to 100

The requirements of the DGHM guideline for surgical hand disinfection are satisfied by the aforementioned formula both in their immediate action and also in their long-term action.

A formulation which contains neither phenethyl alcohol nor 2,2-dimethyl-3-(3-methylphenyl) propanol (3) does not satisfy these requirements.

9. Effectiveness against M. terrae S in the germ carrier experiment with standard cotton

Standard formulation:

- Rewopal MPG 40 25.0%
- aromatic alcohol 2.0 %
- dem. water to 100

Test germ: Mycobacterium terrae ATCC 15755

Test method: Production of the germ carriers: To prepare the germ carriers, standard cotton fabric is used which has been thoroughly rinsed in double-distilled water. The fabric is cut into pieces measuring approximately 1 cm^2, sterilized in a autoclave and dried.

Production of the bacterial suspension:

The bacteria are elutriated with 5 ml CSL from a 24 h-old (37°C) culture onto CSA plates measuring approx. 9 cm in diameter, the suspension being diluted with CSL if necessary. The number of CFU/ml is to be determined using surface culture. It should be > 10^9/ml.

Procedure for the germ carrier test:

The sterilized and dried germ carriers are introduced into the bacterial suspension and left in it for 15 minutes, during which they are turned over twice.

A number (4) of contaminated, thoroughly impregnated germ carriers, corresponding to the proposed removal times - 15, 30, 60 and 120 minutes - is placed in a small dish and 10 ml of the disinfectant solution to be tested in WSH are poured over them. Air bubbles are to be removed by repeated turning of the germ carriers.

After the corresponding action times, the germ carriers are to be removed from the disinfectant solution, and after rinsing twice in each case for 1 min in 10 ml ML solution (see Appendix) to which the deactivating substances were optionally added, the germ carriers are placed onto the surface of a Löwenstein-Jensen nutrient medium with tweezers and moved backwards and forwards 3 to 4 times using light pressure. After inoculating the nutrient medium surface the small cloth is to remain lying directly above the condensed water level of the nutrient medium.

Germ carriers pre-treated in the same way, but kept in WSH for 120 minutes instead of in disinfectant solution are to be inoculated as a control. The inoculated tubes are incubated at 37°C for 3 weeks.

Data expressed qualitatively:

E	individual colonies	++	moderate growth
M	several colonies	+++	heavy growth
+	weak growth	++++	very heavy growth
∞	lawn growth		

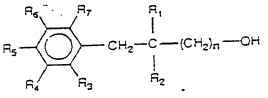
Alcohol	15′	30′	60′	120′
none	∞	∞	∞	∞
1	+ + + +	+ + + +	+ + +	+ + +
2	+ + +	+ +	+	M
3	+ + +	+	+	E
7	+ + +	+ +	+ +	+
8	+ + +	+ +	+	E

The alcohols according to the invention, particularly 2, 3 and 8, show a very good action against mycobacteria with relatively long action times and are therefore suitable for use in instrument disinfectants. The parent compound 1 shows a very much weaker action.

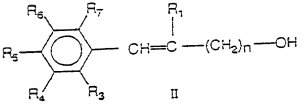
P 42083 vH
January 1997

Patent claims

1. A compound of formula I or II,



I



II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

with the proviso, that in compounds of formula I

i) where R_1 and all groups R_3 to R_7 are hydrogen, then n = 2;

AMENDED SHEET

ii) where R_1 and R_2 are C_1-C_6 alkyl and a) all groups R_3 to R_7 are hydrogen or b) R_5 is methyl, methoxy or chloride and all other groups R_3, R_4, R_6 and R_7 are hydrogen, then n =2;

iii) where R_1, R_2 and R_4 are methyl and all groups R_3 and R_5 to R_7 are hydrogen, then n =2;

iv) where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is methyl, isopropyl, tert. butyl or methoxy, then n = 2;

v) where R_1, R_3, R_6 and R_7 are hydrogen, R_2 is methyl and R_4 and/or R_5 are H or C_1-C_6 alkyl, then n = 2;

vi) where R_1 and R_4 to R_7 are hydrogen, R_2 is methyl or ethyl and R_3 is methyl or methoxy, then n = 2;

vii) where R_1, R_3, R_5 and R_7 are hydrogen, R_2 is methyl, R_4 and R_6 are methyl or R_4 is hydrogen and R_6 is methyl, then n = 2;

viii) where R_1 is hydrogen, R_2 is butyl, R_3 and R_5 are chloride and all other groups R_4, R_6 and R_7 are hydrogen, then n = 2;

and with the proviso, that in compounds of formula II

ix) where R_1 is C_1 - C_5 alkyl or allyl and all other groups R_3 to R_7 are hydrogen, then n = 2, and

x) where R_1 is methyl, R_5 is methyl and all other groups R_3, R_4, R_6 and R_7 are hydrogen, then n = 2.

AMENDED SHEET

ii) where R_1 and R_2 are C_1-C_6 alkyl and a) all groups R_3 to R_7 are hydrogen or b) R_5 is methyl, methoxy or chloride and all other groups R_3, R_4, R_6 and R_7 are hydrogen, then n =2;

iii) where R_1, R_2 and R_4 are methyl and all groups R_3 and R_5 to R_7 are hydrogen, then n =2;

iv) where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is methyl, isopropyl, tert. butyl or methoxy, then n = 2;

v) where R_1, R_3, R_6 and R_7 are hydrogen, R_2 is methyl and R_4 and/or R_5 are H or C_1-C_6 alkyl, then n = 2;

vi) where R_1 and R_4 to R_7 are hydrogen, R_2 is methyl or ethyl and R_3 is methyl or methoxy, then n = 2;

vii) where R_1, R_3, R_5 and R_7 are hydrogen, R_2 is methyl, R_4 and R_6 are methyl or R_4 is hydrogen and R_6 is methyl, then n = 2;

and with the proviso, that in compounds of formula II

where R_1 is C_1 - C_5 alkyl or allyl and all other groups R_3 to R_7 are hydrogen, then n = 2.

2. A compound according to claim 1, in which

in which

R_2 is selected from C_1-C_5 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_5 alkenyl and C_2-C_5 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is hydrogen, fluorine, chlorine or bromine.

3. A compound according to claim 1 or 2 in which
R_2 is methyl ethyl, ethenyl, propyl, propenyl, propargyl, butyl and amyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, is hydrogen, methyl-X-, ethyl-X-, ethenyl-X-, propyl-X-, propenyl-X-, propargyl-X, isopropyl-X, isopropenyl-X-, t-butyl-X-, methoxymethyl-X-, methoxyethyl-X-, ethoxymethyl-X-, ethoxyethyl-X-, methoxypropyl-X- or ethoxypropyl-X-, where X is -O- or -S-.

4. A compound according to any of the preceding claims in which n = 1.

5. A compound according to one of claims 1 to 4 which is (±)-2-(3-chlorobenzyl) butanol.

6. Composition which contains at least one compound of formula I or II according to one of claims 1 to 5 and a compound selected from alcohols, surfactants and solvents.

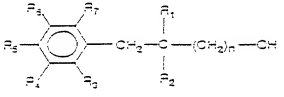
7. Composition according to Claim 6 which contains a compound of formula I or II in a quantity of 0.01 to 10 % by wt., in particular 0.05 to 8 % by wt. and preferably 0.1 to 5 % by wt.

8. Composition according to claim 6 or 7 which contains
a) 0.01 to 10 % by wt. of a compound of formula I or II, and

b) 0.1 to 90 % by wt. of a compound selected from C_1-C_6 alkyl alcohols, unsubstituded or substituted with a C_6-C_{12} aryl, aralkyl or aryloxy group, anionic, cationic, amphoteric or nonionic surfactants, dimethylform-amide, betaines and glycerine.

9. Composition according to any of claims 6 to 8 which is a disinfectant, antiseptic, antimycotic, deodorant or preservative.

10. Process for the production of a compound of formula I according to claim 1



I

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

wherein

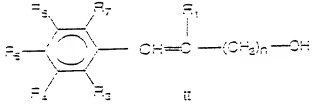
a) a malonic acid dialkyl ester is monoalkylated, as a result of which the group R_2 is introduced,

b) the monoalkylated malonic acid alkyl ester is dialkylated with a benzyl halide optionally substituted at the aromatic ring, as a result of which the groups R_3 to R_7 are introduced, provided they are not hydrogen,

c) the dialkylated malonic acid dialkyl ester is saponified and decarboxylated, as a result of which the correspondingly 3-aryl-substituted propionic acid results and

d) this 3-aryl-substituted propionic acid is reduced with the formation of the desired alcohol of formula I.

11. Process for the production of a compound of formula II according to claim 1



II

in which

R_1 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

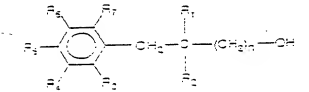
each of R_3 to R_7, independently, is a significance of R_1, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

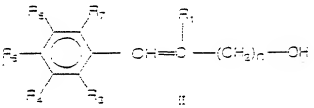
n is 1 or 2,

wherein in the case of n = 1 a corresponding aromatic aldehyde is condensed with an anhydride with simultaneous decarboxylation and then the resulting acid is reduced with lithium aluminium hydride, or in the case of n = 2 the tosy-

late of the respective alcohol with n = 1 is substituted nucleophilically by NaCN and is saponified and the resulting acid is reduced with lithium aluminium hydride to give the desired alcohol.

12. Use of a compound of formula I or II





in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2,

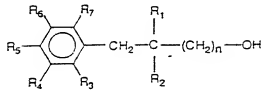
as biocidal active ingredients,

with the proviso, that in compounds of formula I

where R_1 and all groups R_3, R_4, R_6 and R_7 are hydrogen and R_5 is isopropyl, tert. butyl, then n = 2.

Abstract

Biocidal alcohols of general formulae I and II are described



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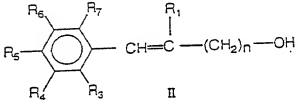

II

in which

R_2 is selected from C_1-C_8 alkyl, uninterrupted or interrupted by oxygen and/or sulphur atoms, C_2-C_8 alkenyl and C_3-C_8 alkynyl,

R_1 is a significance of R_2, independently of R_2, or in compounds of formula I is hydrogen,

each of R_3 to R_7, independently, is a significance of R_2, optionally attached to the aromatic ring by -S- or -O-, is H, halogen, nitrile or thiocyanate, and

n is 1 or 2.

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the **INVENTION ENTITLED** "BIOCIDAL ALCOHOLS, THEIR PRODUCTION AND THEIR USE" the specification of which was filed on June 19, 1997 in the U.S. Patent and Trademark Office.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S)			Date first Laid-	Date Patented	Priority Claimed	
Number	Country	Day/MONTH/Year Filed	open or Published	or Granted	Yes	No
P 44 47 361.3	Germany	21, December 1994			X	

I hereby claim domestic priority benefit under 35 U.S.C. 120/365 of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S)		Status	Priority Claimed	
Application No. (series code/serial no.)	Day/MONTH/Year Filed	pending, abandoned, patented	Yes	No
PCT/EP95/05068	20, December 1995	Pending	X	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. I hereby appoint Farkas & Manelli P.L.L.C., 1233 20th Street N.W., Suite 700, Washington, D.C. 20036-2396, telephone number (202) 778-1310 to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete names/numbers below of persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Farkas and Manelli in writing to the contrary.

Jeffrey S. Melcher 35950 Lawrence Harbin 27644
Edward J. Stemberger 36017 William H. Bollman 36457

1. INVENTOR'S SIGNATURE: X Ralf Berscheid Date X July 06, 1997
Inventor's Name (typed) Ralf Berscheid Germany
First Middle Initial Family Name Country of Citizenship
Residence (City) Hamburg (State/Foreign Country) Germany
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2. INVENTOR'S SIGNATURE: X Date X
Inventor's Name (typed) Heinz Eggensperger Germany
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Residence (City) Hamburg (State/Foreign Country) Germany
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3. INVENTOR'S SIGNATURE: X Wolfgang Beilfuss Date X July 01, 1997
Inventor's Name (typed) Wolfgang Beilfuss Germany
First Middle Initial Family Name Country of Citizenship
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4. INVENTOR'S SIGNATURE: X Sabine Behrends Date X July 01, 1997
Inventor's Name (typed) Sabine Behrends Germany
First Middle Initial Family Name Country of Citizenship
Residence (City) Pinneberg (State/Foreign Country) Germany
Post Office Address (Include Zip Code) Datumer Chausse 170, D-25421, Pinneberg

5 INVENTOR'S SIGNATURE: X Burghard Puchstein Date X July 01, 1997
Inventor's Name (typed) Burghard Puchstein Germany
First Middle Initial Family Name Country of Citizenship
Residence (City) Hamburg (State/Foreign Country) Germany
Post Office Address (Include Zip Code) Edwin-Scharff-Ring 60, D-22309, Hamburg

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED "BIOCIDAL ALCOHOLS, THEIR PRODUCTION AND THEIR USE" the specification of which was filed on June 19, 1997 in the U.S. Patent and Trademark Office.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S)			Date first Laid-open or Published	Date Patented or Granted	Priority Claimed	
Number	Country	Day/MONTH/Year Filed			Yes	No
P 44 47 361.3	Germany	21, December 1994			X	

I hereby claim domestic priority benefit under 35 U.S.C. 120/365 of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S)		Status	Priority Claimed	
Application No. (series code/serial no.)	Day/MONTH/Year Filed	pending, abandoned, patented	Yes	No
PCT/EP95/05068	20, December 1995	Pending	X	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. I hereby appoint Farkas & Manelli P.L.L.C., 1233 20th Street N.W., Suite 700, Washington, D.C. 20036-2396, telephone number (202) 778-1310 to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete names/numbers below of persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Farkas and Manelli in writing to the contrary.

Jeffrey S. Melcher	35950	Lawrence Harbin	27644
Edward J. Stemberger	36017	William H. Bollman	36457

1. INVENTOR'S SIGNATURE: X Date X

Inventor's Name (typed)	First	Middle Initial	Family Name	Country of Citizenship
	Ralf		Berscheid	Germany
Residence (City) Hamburg		(State/Foreign Country) Germany		
Post Office Address (Include Zip Code) Ohlendorffs Tannen 17, D-22359, Hamburg				

2. INVENTOR'S SIGNATURE: X Heinz Langsperger Date X July 09, 97

Inventor's Name (typed)	First	Middle Initial	Family Name	Country of Citizenship
	Heinz		Langsperger	Germany
Residence (City) Hamburg		(State/Foreign Country) Germany		
Post Office Address (Include Zip Code) Alsterallee 13, D-22397, Hamburg				

3. INVENTOR'S SIGNATURE: X Wolfgang Beiß Date X July 01, 1997

Inventor's Name (typed)	First	Middle Initial	Family Name	Country of Citizenship
	Wolfgang		Beiß	Germany
Residence (City) Hamburg		(State/Foreign Country) Germany		
Post Office Address (Include Zip Code) Timmkoppel 39, D-22339, Hamburg				

4. INVENTOR'S SIGNATURE: X Sabine Behrendt Date X July 01, 1997

Inventor's Name (typed)	First	Middle Initial	Family Name	Country of Citizenship
	Sabine		Behrendt	Germany
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